UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/863,158	05/23/2001	David J. Ecker	ISIS-4766	9473

32650 7590 01/31/2006

WOODCOCK WASHBURN LLP
ONE LIBERTY PLACE - 46TH FLOOR
PHILADELPHIA, PA 19103

EXAMINER	
SODERQUIST, ARLEN	
ART UNIT	PAPER NUMBER
1743	

DATE MAILED: 01/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/863,158	Applicant(s) ECKER ET AL.	
	Examiner Arlen Soderquist	Art Unit 1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-32,34-40 and 42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-32,34-40 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

2. Claims 26-29, 32, 34-40 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kempe (US 5,514,789) in view of Baldeschwieler (US 5,847,105) or alternatively Baldeschwieler in view of Kempe. In the patent Kempe describes a methods for Oligonucleotide synthesis and cleavage. In example 6 a method using membrane-bottom wells is described. In the method a microtiter well plate is fitted with a frit at the bottom of the plate in order to retain a loose support of polystyrene, controlled pore glass or any material suitable for a solid phase synthesis procedure. The loose support is in particle or membrane form. The frit may itself be of a type that can be functionalized with nucleoside and thus serve as both solid synthesis support and filter. A typical sequence for the synthesis and processing on such microplates involves the following steps: (1) a functionalized support is placed in the wells of the microplate or the filters of the microplate are functionalized; (2) the support is washed and dried with a solvent like acetonitrile; (3) the protecting group of the nucleotide bound to the support is removed with a suitable reagent; (4) the washing step is repeated; (5) a reactive nucleoside or nucleotide is introduced into the wells; (6) the reaction mixture is allowed to react followed again by washing; (7) the product is converted into a stable phosphate triester; (8) capping is performed for non-reactive groups of the next cycle; (9) steps 2-8 are repeated until the final product has been synthesized and (10) the completed product is cleaved and recovered. The microplate can contain loose support material, typically CPG or polystyrene or a membrane

with functionalized nucleoside. A membrane can also serve as a frit or filter for the plate. The 5'-hydroxyl group is available for coupling to another nucleotide with a 5'-hydroxyl protecting group which can be removed during synthesis. After washing, the solvent is removed from the wells by any suitable means, e.g., using pressure in the chamber to push the solution through the frit, or the plate itself is centrifuged to remove the solvent. The reaction time is typically 5 to 200 seconds, as deemed necessary for the reaction conditions used. The mixture can be agitated to improve the distribution of reagents. Typically the DNA can be synthesized in varying sizes of about 5 nucleotides up to over 100 nucleotides. The elution of the final cleaved, deprotected DNA product from the microplate can be accomplished by centrifugation, pressure or gravity and be collected into another plate underneath the synthesis plate. The paragraph bridging columns 6-7 teaches the possibility of incorporating many of the liquid handling approaches that are common in protein and/or DNA synthesis and especially those that are automated. Kempe does not teach jetting the various solutions onto the support.

In the patent Baldeschwieler teaches method and apparatus for performing multiple sequential reactions on a matrix. In the method a substrate is prepared upon which microdrop-sized loci are located at which chemical compounds are synthesized or diagnostic tests are conducted. The loci are formed by applying microdrops from a dispenser from which a microdrop is pulse fed onto the surface of the substrate. Column 1 lines 14-25 teach that the apparatus and method are useful for performing a test or synthesis involving sequential steps such as DNA sequencing, DNA diagnostics, oligonucleotide and peptide synthesis, screening tests for target DNA, RNA or polypeptides, synthesis of diverse molecules, DNA separation technology whereby DNA binds to target molecules, preparation of polysaccharides, methods for making complementary oligonucleotides, and any other test, sequencing or synthetic method utilizing a sequence of steps at a locus. Lines 27-53 of column 1 teach that a disadvantage with previous synthesis methods are that the entire support must be exposed to a single reagent. Also taught is the object of providing a method in which a plurality of different sequential reactions can be performed on a support (substrate) at a plurality of microdrop sized loci. An advantage or improvement can be obtained by providing loci so that combinations of different reactions may be conducted on the same matrix. The summary of column 2 teaches how the synthesis steps are performed. In the case of delivery of reagents that become attached to the surface, the invention

provides a substrate having a surface to which a first reagent can be attached by dispensing microdrops of the reagent in liquid form onto the substrate. The dispenser is displaced relative to the surface and at least one microdrop is applied thereto containing the same or a different reagent. By repeating this using the same or a different first reagent in liquid form, a plurality of loci on the surface may be prepared wherein the reagents covalently attach at microdrop-sized loci wherein the boundaries of each locus are not contiguous to any adjacent locus. The surface may then be washed to remove unattached reagent. If needed, the entire surface may be treated, or alternatively, a selected subset of loci may be treated, with deprotecting reagents to expose reactive sites of the molecules attached to the surface. The deprotecting reagent may also be dispensed from the device. Then one or more microdrops containing a second reagent in liquid form may be dispensed at selected loci on the substrate surface, whereby the second reagent is selected to react with the molecules already attached to the matrix. The dispenser is again displaced relative to the surface to apply the second reagent at different loci using the same or a different second reagent which reacts with the respective attached molecules. Again, the entire surface will be washed to remove unreacted second reagents. Then the entire surface or selected subsets of loci may be treated with deprotecting agents, and this process may be repeated. Column 3, lines 27-33 teach the substrate as a solid, such as glass, prepared to receive linkers attached to the surface. Porous substrates, such as paper or synthetic filters may be used, as well as filters having straight, parallel micropores (such as sold by Nucleopore). In such a microporous substrate, the reactions may take place within the pores, thus amplifying the potential signal at the locus. Column 6 lines 46-67 discuss the ink-jet used to dispense the microdroplets. Column 3, lines 4-14 of Baldeschwieler discuss the removal of the formed compounds either selectively or non-selectively for diagnostic assays or isolation of the final compound(s). This removal is through cleavage reagents that also may be dispensed as microdroplets. Column 5, lines 60-65 teach the placement of portions of the substrate containing one locus in microtiter wells for diagnostic or therapeutic tests. Baldeschwieler does not teach the synthesis occurring in wells of a shaped body.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the dispensing means of Baldeschwieler into the method of Kempe because of the advantages of performing multiple reactions on the same support as taught by

Baldeschwieler. In the alternative, it would have been obvious to one of ordinary skill in the art at the time the invention was made to place the supports for chemical synthesis in wells of a shaped body as taught by Kempe in the method of Baldeschwieler because of the advantages being able to directly process the substrate or chemical thereon without an intermediate cutting step or with supports that would not have been easy to divide and come in particle form as shown by Kempe.

3. Claims 26-27, 29, 32, 34-40 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saxinger in view of Kempe (as discussed above), Baldeschwieler (as discussed above) and Salmon. In the published application Saxinger teaches automated peptide design and synthesis in which the peptides are synthesized on interior, inward facing surfaces of reservoirs formed in a solvent resistant substrate. Page 6, lines 2-10 define a "solvent resistant substrate" as a substrate that is insoluble and inert to solvents commonly utilized in the synthesis of peptides; and which also allows for the eventual anchoring or attachment of a peptide thereto. Such substrates would include, for example, polyolefins such as polyethylene and polypropylene, glass, DELRIN (a linear polyoxymethylene-type acetyl resin), and Costar TPX (polymethyl-pentene). Lines 20-30 define "reservoir" as an indentation, impression, cavity, sunken area or the like, in a solvent resistant substrate, wherein the indentation, etc., is capable of receiving and holding an appropriate quantity of a desired solution. The term is also meant to include those reservoirs having a portion of their inward surface as a filter type surface, for example, a bottom surface could be a filter through which liquids could be removed when desired. Page 9, line 30 to page 10, line 25 teach that the term "microtiter format" is used for discussing a preferred embodiment of a solvent resistant substrate. This is not meant to lessen the general applicability of procedures disclosed to suitable substrates having other "formats". The procedures are as applicable to building a peptide in, for example, a single "test tube" made of a suitable material, as they are to building distinct and different peptides in each well of a suitable "solvent resistant" microtiter plate substrate having multiple wells therein. It was that other suitable substrates are available including a substrate having a filter as a portion thereof as, for example, the bottom of a reservoir could be a filter disk, made of a material, so that liquid reagents could be easily removed from a reservoir when desired. All of the substrate configurations are potentially valuable since the only principle requirements for the substrate are that it is composed of a

suitable solvent resistant material and that one or more reservoirs exist in the substrate with at least a portion of an interior, inward facing surface activated for the attachment (or anchoring) of a protected carboxyl terminal amino acid. Page 13 lines 19-31 teach the ability of cleaving the functional group on the substrate. Page 16, lines 12-27 and page 17, lines 16-24 teach the automated control of synthesis of up to 96 different peptides. Figure 2(A) and 2(B) and their respective discussions show and describe flow charts for this automated method. Page 22, lines 6-20 teach that the peptides may be cleaved after synthesis and that the techniques and methods taught are also applicable to synthesis of other organic molecules or macromolecules including sugars and oligonucleotides (RNA and DNA). Example 1 gives an example of this method. Of note is that page 23 lines 14-21 teach alternative systems including beads or porous filters. Saxinger does not teach jetting the various solutions onto the support, placement of a loose support in the reservoirs or a collection plate to collect the synthesis products.

In the paper Salmon teaches discovery of biologically active peptides from a library synthesized on solid supports. Pages 11709 and figure 3 teach the two-stage release of the peptide from the support for testing purposes. In the method a plurality of beads is first added to wells (donor chambers) of a 96-well microassay filtration plate. A portion of the bound peptide is released from the support and transferred from the filtration plate to a corresponding assay plate (acceptor chambers) and reagent is added. The beads from wells that a reaction with the reagent occurred are then individually loaded into wells of a microassay filtration plate and the additional peptide is released, transferred to a corresponding assay plate and a reagent added. In the paragraph bridging pages 11711 and 11712 Salmon teaches fluid volumes for the wells can be in the range of 10 - 100μl.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the dispensing means of Baldeschwieler into the method of Saxinger because of the advantages of performing multiple reactions on the same support as taught by Baldeschwieler. It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate a collection or assay plate into the methods of Saxinger because of the ability to carry out further tests on the synthesized materials or to isolate the individual compounds for analysis as taught by Salmon, Kempe and Baldeschwieler.

Additionally Kempe shows the equivalence/obviousness of using a loose support or the filter at the bottom of a reaction well, as found in the Saxinger teachings, as the support for the synthesis.

4. Claims 28 and 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saxinger in view of Kempe, Baldeschwieler and Salmon or Kempe in view of Baldeschwieler as applied to claims 26-27, 29, 32, 34-40 and 42 above, and further in view of the admitted state of the prior art and/or Koester (US 4,923,901). Kempe and Saxinger do not teach the full scope of the support materials.

Page 15, line 22 to page 16, line 3 of the instant specification teach that several of the possible support are either known or commercially available. Specifically, supports include CPG (controlled pore glass) available from various distributors including CPG Inc./Millipore Corp.; RAPP copolymer, a highly crosslinked polystrene, sold as TentaGel or a like product HLP (high loaded polystrene) sold by ABI Corp.; Primer Support, a highly crosslinked polystrene, sold by Pharmacia; POROS-OS polystrene sold by PerSeptive, MPG (a magnetic pore glass) sold by CPG Inc.; Nucleic Acid Membrane Support sold by Millipore. Other useful supports include membranes sold by the Amicon division of W. R. Grace, Inc., and those sold by Gelman Sciences. Other membrane supports include membranes as described or referenced in U.S. Pat. No. 4,923,901 (Koester) assigned to Millipore Corp.; various supports as described in patent application WO 94/05394 and references cited therein; and various supports as described in patent application WO 90/02749 including activated polystrene layer on a polyethylene membrane (this list includes at least the synthetic filters of Baldeschwieler).

The Koester patent was sited in the instant specification as disclosing supports usable for the instant methods. More specifically Koester teaches a method for synthesizing oligonucleotides and peptides directly onto a membrane. The method provides a means for generating membrane affinity supports. A modified membrane for the method of direct synthesis is also provided. The introduction of the patent teaches various supports that are known to be used in solid phase peptide and oligonucleotide synthesis. These supports include beaded material such as cellulose, glass beads, Sephadex, Sepharose, agarose, polyacrylamide, porous particulate alumina, hydroxyalkyl methacrylate gels, diol-bonded silica or porous ceramics, flat material such as filter disc of nylon and nitrocellulose, glass beads of controlled porosity. A membrane, a being flat and highly porous, mechanical stable material, would be most

advantageous as affinity support, because it could be handled easily, cut into various sizes, stacked on top of each other for upscaling purposes and reused several times. Furthermore, the support should be chemically stable under the conditions of oligonucleotide and peptide synthesis and should not show non-specific binding of either nucleic acids or proteins as this would give rise to a sensitivity-reducing background interaction. The membranes of Koester are taught as fulfilling these requirements or providing these advantages (this list also includes at least the synthetic filters of Baldeschwieler).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the admitted known synthesis supports or those of Koester into the methods of Saxinger or Kempe because of the known advantages of the porous supports as taught by Koester and the fact that the respective lists at least include the synthetic filters of Baldeschwieler and as shown by Koester the materials are known as supports for synthesis of oligonucleotides.

5. Applicant's arguments filed November 14, 2005 have been fully considered but they are not persuasive. First the office action contains a new ground of rejection (Baldeschwieler in view of Kempe). Relative to the maintained rejections examiner presents the following comments. First, the applied references are all generally dealing with the same thing, synthesis of a compound on a support or substrate. Thus there is a clear basis for a reasonable expectation of success. For example, in the Baldeschwieler patent the reagents are jetted on a location. If the device of Baldeschwieler were used to jet droplets on individual supports in a microtiter plate, it would have been a simple ting to place the location in the control program of Baldeschwieler. Additionally since the synthesis of Baldeschwieler taught for a number of different substrates/supports, there is an expectation of success for the synthesis working on the supports of Kempe if they were deposited directly in droplet form as taught by Baldeschwieler. Relative to the cleavage by gas in the Kempe reference examiner would point to two sections of the reference. The first is column 1, lines 56-64, teaching that reagents and conditions useful for cleavage depend on the nature of the linkage. In this section ester linkages are taught as the type that are cleavable with concentrated ammonium hydroxide. It is noted that examiner was not able to find a disclosure of another type of linkage that would be cleaved by the gaseous ammonia. Thus there are types of linkages that there is not an equivalent gaseous cleavage agent

and some form of liquid agent would be required. Second, the paragraph bridging columns 6-7 teaches the possibility of incorporating many of the liquid handling approaches that are common in protein and/or DNA synthesis and especially those that are automated. This clearly invited one of skill in the art to use known liquid handling methods for their known advantages. The last sentence of the paragraph teaches that these machines will compete well with those presently available that use aqueous ammonium hydroxide cleavage. Here again is a reference or teaching that would indicate that this patent is lacking when it comes to other types of liquid cleavage agents. Baldeschwieler clearly shows that it is capable of handling all types of liquid cleavage agents. Thus by incorporation of the Baldeschwieler liquid handling, one of skill in the art would have recognized that the device would have been able to handle liquid cleavage agents increasing the scope of its utility. Examiner also notes that the gaseous cleavage of agent of Kempe is formed by heating a solution of the ammonium hydroxide cleavage agent or is derived from a liquid cleavage agent. Relative to the combination based on Saxinger examiner points out that the advantage was based on the microtiter format and the existence of commercially available apparatus to automate the transfer of reagents. If applicant is trying to argue that the apparatus of Kempe or Salmon are not in the microtiter format. In this regard applicant is directed to example of Kempe 6 which clearly shows a microtiter well plate being used. In the Salmon reference, the paragraph bridging the columns of page 11709 clearly teaches 96-well filtration plates that are on a microtiter format. Thus the substitution of the filtration plate would have been recognized as fully within the scope of what Saxinger taught and there is no difficulty in using the plates of Kempe or Salmon. Relative to the recitation of claim 1 Saxinger, while it might be a preferred embodiment, it is clearly not the only embodiment possible. As an example claims 17-20 do not limit the form of the reservoir and could include a filtration plate type reservoir with a support therein. Relative to the first and second surfaces, the instant claims are not limited to any shape for the surfaces and a microtiter plate has a top or first surface and a bottom or second surface. Thus the arguments are not persuasive.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose telephone number is (571) 272-1265. The examiner's schedule is variable between the hours of about 6:30 AM to about 5:00 PM on Monday through Thursday and alternate Fridays.

A general phone number for the organization to which this application is assigned is (571) 272-1700. The fax phone number to file official papers for this application or proceeding is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Arlen Soderquist

Arlen Soderquist
Primary Examiner